REMARKS

Prior to entry of this amendment, claims 1, 2, 6 and 9-50 are pending in the application; of these, claims 17, 18, and 20-46 are withdrawn from consideration. Claims 1, 2, 6, 9-16, 19, and 47-50 stand rejected, as discussed below.

By this amendment, claims 1, 6, 9, 15, 16, 22, 23, 47, and 50 are amended; claims 2, 12, 14, 24-34, 35-46, 48, and 49 are cancelled; and new claims 51-63 are added. No new matter is added by this amendment. Applicants reserve the right to pursue protection of any subject matter deemed to be removed from consideration by this amendment in a related case.

Entry of this amendment and reconsideration of the claims is respectfully requested. It is believed that entry of this amendment after final rejection is proper because it cancels claims, introduces claims that are believed to be allowable, and otherwise streamlines the claim set for appeal if such becomes necessary.

After entry of this amendment, **claims 1, 6, 9-11, 13, 15-23, 47, and 50-63 are pending**. Of these, claims 17, 18, 20, 21, and 23 are withdrawn from consideration. By the amendments made herein, claim 23 has been amended to fit within the elected group in that it depends from claim 1. Applicants therefore ask that claim 23 be entered into examination and considered by the Examiner.

Written Description rejection under 35 U.S.C. §112, first paragraph

Claims 1, 2, 6, 9-16, 19, and 47-50 are rejected as containing subject matter which allegedly is not described in the specification in such a way to convey that the inventors had possession of the claimed invention. Applicants understand that this written description rejection rests on concern that the claimed method employs a "genus of TRAC1 polypeptides" that is too broad (in that there is allegedly insufficient structure-function limitation to the genus) in view of Applicants' allegedly insufficient disclosure in the specification of multiple species within this genus. Applicants traverse this rejection, to the extent it would be maintained after entry of this amendment.

The claimed methods currently employ a genus of isolated recombinant polypeptides that comprise "a TRAC1 polypeptide with an amino acid sequence having at least about 90% identity to the amino acid sequence of SEQ ID NO: 1, wherein the TRAC1 polypeptide has ubiquitin ligase activity" (*e.g.*, claims 1 and 55, and claims that depend therefrom). This genus encompasses polypeptides (such as fusion polypeptides) that include a functional TRAC1 polypeptide that is defined both by structure (at least about 90% sequence identity to SEQ ID NO:1) and a function that is related to and dependent on that structure (ubiquitin ligase activity). This is not an unreasonable breadth, particularly in view of the teachings in Applicants' specification and the knowledge of those of ordinary skill in the art.

Applicants' specification describes functional domains of the TRAC1 polypeptide, and in particular describes the TRAC1 Ring finger domain in the context of other known Ring finger domains (see, *e.g.*, Figure 13 and accompanying text in the specification). Applicants also specifically demonstrate that the Ring finger domain is essential for TRAC1 activity, while the C-terminal region (absent in the described truncation Hit(TRAC-ΔC) is not needed for ubiquitin ligase activity (see, *e.g.*, the Summary of Functional Effects provided in Figure 17).

The Office (at page 4 of the pending action) alleges that only one species of the genes of TRAC1 polypeptides has been disclosed. In fact, this is not the case. In addition to the wild-type TRAC1 polypeptide (SEQ ID NO:1 and Figure 1A), applicants also disclose mouse wild-type TRAC1 (SEQ ID NO:7 and Figure 1F). Applicants also provide the nucleic acid sequence of a specific truncated human TRAC1 (SEQ ID NO:4 and Figure 1D), also referred to as Hit(TRAC1-ΔC) and is shown to have TRAC1 ubiquitin ligase activity (see, *e.g.*, Figures 11B, 12A, 12B). Point mutations are also provided, particularly in the context of demonstrating that the Ring finger domain is necessary for TRAC1 ubiquitin ligase activity. See, *e.g.*, data presented in Figure 13B.

Further, it is noted that the data shown, for instance, in Figures 12B and 13B was generated using a fusion polypeptide that includes both TRAC1 (or a truncated TRAC1) and a label. These are therefore representative of that portion of the genus of polypeptides that is directed to fusion proteins. Applicants' specification also teaches other possible fusions between TRAC1 and other polypeptides, thereby providing broader written description for this portion of the genus.

At the end of this rejection, the Office references the "revised guidelines", which Applicants understand to be the Written Description Guidelines (Federal Register, vol. 66. No. 4, January 5, 2001, pages 1099-1111). Applicants note the Guidelines state that, for each claim drawn to a genus, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics." It is accordingly clear that an actual reduction to practice of **each and every** species within a claimed genus is not a requirement of the Guidelines. This is made explicitly clear in the materials which accompanied the Guidelines, responding to comments received in response to the draft Guidelines, wherein it is stated (emphasis added) that "The Guidelines have been clarified to state that *describing an actual reduction to practice is one of a number of ways to show possession of the invention*. Description of an actual reduction to practice offers an important 'safe haven' that applies to all applications and is *just one of several ways by which an applicant may demonstrate possession of the claimed invention*." Further, Applicants note that Example 18 in the Training Material that accompany the Guidelines is illustrative of the fact that, where there is an actual reduction to practice of even a single embodiment, a claim which encompasses a relevant genus may nevertheless be fully supported and adequately described.

The fact that not every species within a genus needs to be enumerated is further emphasized in MPEP § 2163(II)(A)(3)(a)(ii), which states that "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces."

Applicants' specification contains an explicit description of a representative number of species, and it is not required that Applicants provide "individual support of each species" in the genus. In addition, the breadth of the genus is reasonable in view of Applicants' teachings and the high level of skill in the art. Applicants respectfully submit that the written description requirement for a genus of TRAC1 polypeptides currently employed in the claims has been fulfilled as the description clearly contains a sufficient description of TRAC1 polypeptides (and variants and a truncation thereof) by actual reduction to practice. Furthermore, the skilled person would recognize from the disclosure that

the Applicants were in possession of the claimed genus at its current breadth. Applicants request that the written description rejections be withdrawn.

Enablement rejection under 35 U.S.C. §112, first paragraph

Claims 1, 2, 6, 9-16, 19, and 47-50 are further rejected as the specification allegedly does not provide enablement for "any method comprising contacting a compound (any small organic) with any TRAC1 polypeptide comprising an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 1, having any ligase activity and determining any functional effect of the compound upon the TRAC1 polypeptide." Applicants traverse this rejection, to the extent it would be maintained after entry of this amendment.

The claims as presented herein specify that TRAC1 polypeptide must have ubiquitin ligase activity (rather than "any ligase activity"), and further requires determining the effect (if any) of the compound on the TRAC1 ubiquitin ligase activity (rather than "any functional effect"). It is clear from Applicants specification (and arguments made previously) that enablement is provided for methods dependent on the examination of TRAC1 polypeptide ubiquitin ligase activity (even where the polypeptide includes additional sequence, such as in a fusion protein). Teachings related to several different TRAC1 polypeptides, and assays of their function, are discussed above with regard to the written description rejection.

To the extent that practice of the claims (at their current scope) would require some amount of experimentation, the amount of experimentation is in no way "unnecessarily, and improperly, extensive or undue" as alleged at page 8 of the current Office action. The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation is not undue. *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988). A considerable amount of experimentation is permissible, if it is merely routine or if the specification provides a reasonable amount of guidance in which direction the experimentation should proceed. *Id.*

Applicants submit that any experimentation would be routine and the present application provides the guidance necessary to understand and carry out the methods encompassed by the claims.

For instance, the specification clearly teaches variants of TRAC1 polypeptides having certain percentages sequence identity (*e.g.*, [0067] in U.S. application publication 2002/0146747), assays for modulators of TRAC1 (*e.g.*, [0152] through [0166]), and both direct (*e.g.*, the functional assays disclosed in WO 01/75145, incorporated by reference in the present application) and indirect (*e.g.*, CD69 upregulation, Example 1; and other functional effects as discussed for instance in [0072] – [0073]) assays for TRAC1 ubiquitin ligase activity.

Thus, Applicants contend that the specification provides sufficient guidance for one of skill in the art to understand and perform the claimed methods in order to identify a compound that modulates T lymphocyte activation (and more generally, modulate or inhibit TRAC1 ubiquitin ligase activity). Further, at the time the application was filed it was well known to those of skill in the art how to modify a given protein (*e.g.*, the TRAC1 polypeptide shown in SEQ ID NO:1), for instance by modifying its sequence (up to 10%) and/or by recombinantly joining it to another protein or peptide to form a fusion protein. Thus, Applicants submit that, given the state of the art at the time of filing and the guidance in the specification, it would merely be routine to perform any modifications necessary to practice the entire scope of the claimed methods of identifying a compound that modulates T lymphocyte activation, particularly in view of Applicants' specific teachings in the specification. Applicants therefore request that the enablement rejection of the claims be withdrawn.

Applicants thank the Examiner for pointing out (at page 5 of the pending Office action) that the specification is "enabling for a method comprising contacting a compound (any small organic) with a TRAC1 polypeptide, wherein said TRAC1 polypeptide comprises the amino acid sequence of SEQ ID NO: 1 and determining the functional effect of the compound upon the TRAC1 polypeptide." Applicants draw the Examiner's attention to claims 15 and 57 (as presented herein). These claims specific that the TRAC1 polypeptide has the amino acid sequence of SEQ ID NO: 1.

Rejections under 35 U.S.C. §102

Claims 1, 2, 13, 15, 16, 19 and 47 are rejected under §102(a) as allegedly anticipated by Sitkovsky *et al.* (U.S. Patent No. 5,180,662). Applicant traverses this rejection, to the extent it would be maintained after entry of this amendment.

Applicants strenuously disagree with the assertion that Sitkovsky teaches (explicitly or implicitly) the method as previously claimed. However, in the interests of advancing prosecution of the current case, the claims are amended herein to specify that the methods "for identifying a compound that modulates T lymphocyte activation" are carried out with an isolated recombinant polypeptide and require "determining the effect of the compound upon the TRAC1 ubiquitin ligase activity" (see, *e.g.*, independent claims 1 and 55 as presented herein). Nowhere in Sitkovsky *et al.* is there any teaching of an *in vitro* (that is, cell free) method of identifying a compound that modulates T lymphocyte activation. In addition, there is no teaching in Sitkovsky *et al.* of the TRAC1 polypeptide, let alone that it has ubiquitin ligase activity. Thus, the now-claimed method steps clearly are not the same as the method taught by Sitkovsky *et al.* The cited reference does not and cannot anticipate the pending claims, and Applicants request that this rejection be withdrawn.

Request for Rejoinder of Species

As it is believed that one or more of generic claims will be found allowable, Applicants expressly request rejoinder of the claims directed to compounds "species" not currently under review. These include the species exemplified in claims 17, 18, 20, and 21 (*e.g.*, antibodies, antisense molecules and peptides).

CONCLUSION

It is believed that the claims are now in condition for allowance. If any minor issues remain to be resolved before a Notice of Allowance can be issued, the Examiner is requested to telephone the undersigned at the number shown below before issuing a written response to this paper.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Tanya M. Harding/
Tanya M. Harding, Ph.D.
Registration No. 42,630